consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10017628.

Reconsideration of the application is respectfully requested.

## I. AMENDMENT

Please make the following amendments:

**In the Claims:**

Please cancel claims 2, 3, 6, 12-15, 18-20, 26-42, 44, 45 and 48 without prejudice or disclaimer.

Please amend claims 1, 11 and 43 as follows:

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1. (Twice amended) A homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region, wherein the homoconjugate has anti-neoplastic activity and wherein said monoclonal antibody has substantially no anti-neoplastic activity in an unconjugated form.

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11. (Twice Amended) A method of making a homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region, comprising:

obtaining a first monoclonal antibody that does not comprise an Fc region;

obtaining a second monoclonal antibody that does not comprise an Fc region; and

conjugating the first monoclonal antibody to the second monoclonal antibody, wherein the first and second monoclonal antibodies have anti-neoplastic activity in a conjugated form and have substantially no anti-neoplastic activity in an unconjugated form.



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43. (Twice Amended) A pharmaceutical composition comprising a homoconjugate comprising a monoclonal antibody and a pharmaceutically acceptable carrier, wherein the monoclonal antibody does not comprise an Fc region and wherein the monoclonal antibody has anti-neoplastic activity in a conjugated form and has substantially no anti-neoplastic activity in an unconjugated form.

## II. RESPONSE TO OFFICE ACTION

### A. Status of the Claims

Claims 1-52 were filed in the instant application. Claims 10, 24 and 52 were canceled in Applicants' Response to Office Action mailed in the case on July 14, 2000. Claims 2, 3, 6, 12-15, 18-20, 26-42, 44, 45 and 48 have been canceled herein without prejudice or disclaimer. Claims 1, 11 and 43 have been amended herein. Support for the amended claims can be found in the claims as filed. Therefore, claims 1, 4-5, 7-9, 11, 16-17, 21-23, 25, 43, 46-47 and 49-51 are now pending and presented for reconsideration. For the convenience of the Examiner, attached as Appendix A is a list of the claims as they are believed to appear after entry of the amendments contained herein.

### B. The Rejections Under 35 U.S.C. § 102(b) Are Overcome

#### 1. The Rejection over Ahlem *et al.* Is Overcome

The Action has maintained the rejection of claims 1-6, 11-20, 25, 43-48, and 52 under 35 U.S.C. § 102(b), and newly applied the rejection to claims 7, 21 and 49, as being anticipated by Ahlem *et al.* Specifically, the Action contends that Ahlem *et al.* teaches homoconjugates, for example, in the abstract, at column 2, lines 29-58, at column 6, lines 45-48, at column 9, lines 22-27, and at column 13, lines 65-68. Applicants respectfully traverse.



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The instant amendments clarify the distinction between the claimed invention and the teachings of Ahlem *et al.* As amended, claim 1 is directed to a homoconjugate "..wherein the homoconjugate has anti-neoplastic activity..." Similarly, claim 11 is directed to a method of making a homoconjugate of two or more monoclonal antibodies, "....wherein the first and second monoclonal antibodies have anti-neoplastic activity in a conjugated form and have substantially no anti-neoplastic activity in an unconjugated form." Finally, claim 43 is directed to a pharmaceutical composition comprising a homoconjugate comprising a monoclonal antibody "...wherein the monoclonal antibody has anti-neoplastic activity in a conjugated form and has substantially no anti-neoplastic activity in an unconjugated form."

Ahlem *et al.* does not anticipate the claims. ***The presently claimed homoconjugate itself has anti-neoplastic activity. Unlike the trifunctional compound of Ahlem, this activity is not based on a "therapeutic agent."*** This is because, as described in the specification, Applicants' claimed homoconjugates cause the target cell to undergo cell cycle arrest (hereinafter "CCA") and/or apoptosis through the binding and hypercrosslinking of cell surface antigens to the homoconjugate to elicit a negative signal resulting in sending the target cell into CCA and/or apoptosis. This is in contrast to Ahlem *et al.*, in which the described heteroconjugate is guided to a target antigen based on a first specificity and a therapeutic agent is delivered thereto by way of linked immunologic agent.

Further, the cited reference also does not anticipate the claims because it does not teach ***homoconjugates***. For example, Applicants direct the Examiner to the portions of the Ahlem *et al.* reference cited in the Action as teaching homoconjugates; *e.g.*, at the Abstract, at column 2, lines 29-58, at column 6 lines 45-48 and at column 13, lines 65-68 of Ahlem *et al.* As can be seen, for example, in the Abstract of Ahlem, this reference is directed to ***trifunctional*** "antibody-

like" compounds. The Action alleges that Ahlem teaches that "Fab's can have the same specificity." However, Ahlem *et al.* ***does not teach the instantly claimed homoconjugates***. Ahlem *et al.* only teaches a ***heteroconjugate*** of three antibodies "having from 2-3 differing specificities (functions)." See Col. 1 at lines 15-16. As shown in column 2, lines 29-58 of Ahlem *et al.*, as cited in the Action, at least one of the three components of Ahlem *et al.*'s trifunctional "antibody-like compound of Formula I" is directed to a therapeutic or diagnostic agent. Therefore, ***the construct has at least two specificities***. In contrast, amended claim 1 of the invention is directed to a homoconjugate. The term "homoconjugate" is described in the specification, at page 8, lines 15-17, where it is stated that a "homoconjugate" ***"refers to a conjugate comprised of a single species of monoclonal antibody"*** *(emphasis added)*. Therefore, because the trifunctional compounds of Ahlem *et al.* are made up of more than one species of monolconal antibody, these compounds cannot anticipate the claims.

The other portions of Ahlem *et al.* cited in the Action similarly demonstrate the above distinctions between the reference and the claimed invention. For example, at column 6, lines 45-48, Ahlem *et al.* states that, in Formula I, the three listed elements "are individual Fab'-like fragments wherein two of the fragments may have the same antigenic specificity, but preferably, wherein each fragment has a unique antigenic specificity relative to the others." Therefore, again, this is not a homoconjugate as set forth in the claims. Therefore, Ahlem *et al.* cannot be considered to anticipate Applicants' claimed invention.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-6, 11-12, 15, 20, 25, and 43-48 under 35 U.S.C. § 102(b) be withdrawn.

**2. The Rejection over Cumber *et al.* is Overcome**

The Action has maintained the rejection of claims 1-2, 6, 11-12 and 23 under 35 U.S.C. § 102(b), and newly applied the rejection to claims 7, 21 and 49, as being anticipated by Cumber *et al.* Applicants respectfully traverse, as set forth below.

The cited reference does not anticipate the amended claims. As described in Applicants' prior Response to Office Action, Cumber *et al.* teaches a bivalent (bisFvCys) conjugate and a method to make such conjugate. *See* pg. 125, lns. 2-4. The purpose of creating the bisFvCys conjugate was to test the stability of the construct. See Abstract. However, ***there is no suggestion that the Cumber et al. conjugate has the anti-neoplastic activity of the claimed invention***. At page 120 of Cumber *et al.*, in the second full paragraph, it is indicated that the bisFvCys construct was comprised of two murine ***anti-lysozyme*** Fv fragments. There is no suggestion that the anti-lysozyme construct demonstrates anti-neoplastic activity, as required by the claims. In contrast, the instant amended claims are specifically directed to homoconjugates having anti-neoplastic activity. Therefore, an element expressly set forth in the rejected claims is missing in the cited reference. Because the Cumber *et al.* reference lacks at least one aspect of the claimed invention, the claims are not anticipated.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-2, 6, 11-12, 18-20, and 23 under 35 U.S.C. § 102(b) be withdrawn.

**C. <u>The Rejections Under 35 U.S.C. § 102(e) Are Overcome</u>**

The Action adds a new ground of rejection of claims 1, 3, 9, 11, 13 and 23 under 35 U.S.C. § 102(e) as being anticipated by Bagshawe *et al.*, U.S. Patent No. 5,683,694. In particular, the Action contends that Bagshawe *et al.* teach a conjugate comprising a monoclonal



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antibody that does not comprise an Fc region and exhibits anti-neoplastic activity. The Action also states that Bashawe teaches how to make such a conjugate using a mammalian monoclonal antibody. Applicants respectfully traverse the rejection.

The portions of Bagshawe *et al.* cited in the Action demonstrate that the reference does not anticipate the claims. As described at Column 1, lines 14-20 of Bagshawe, this reference concerns antibody fragments capable of binding a tumor associated antigen and which are bound to an enzyme capable of converting a prodrug into a cytotoxic drug. At column 2, lines 24-40, Bagshawe discusses a "first component" which is a "conjugate of an antibody to a tumor associated antigen or a fragment thereof that includes the antigen binding site of the antibody, wherein the ***antibody or fragment thereof is conjugated directly, or indirectly through a linking component, to an enzyme or to an antibody or fragment with catalytic functions***" (emphasis added). This is in contrast to the ***claimed invention, which contains the limitation that the conjugate exhibits anti-neoplastic activity***. The use of an antibody as ***a targeting molecule for a cytotoxic agent does not anticipate this limitation***, as it is the cytotoxic agent that exhibits the anti-neoplastic activity. In contrast, the homoconjugates created by the inventors were surprisingly found to be capable of causing target cells to undergo cell cycle arrest and/or apoptosis initiated by negative signaling resulting from the binding and hypercrosslinking of cell surface antigens to the homoconjugate. Therefore, because Bagshawe *et al.* lacks at least one aspect of the claimed invention, the claims are not anticipated.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1, 3, 9, 11, 13 and 23 under 35 U.S.C. § 102(e) be withdrawn.

**D. The Rejections Under 35 U.S.C. § 103 over Glennie, Ghetie *et al.* or Boslet *et al.* in view of Wolff *et al.* Are Overcome**

The Action has maintained the rejection of claims 1-3, 6-15, 18-25, 43-45 and 48-51 under 35 U.S.C. § 103, and newly applied the rejection to claims 7, 21 and 49, as being unpatentable over Glennie, Ghetie *et al.*, or Bosslet *et al.*, in view of Wolff *et al.* In particular, the Action alleges that the cited references teach antibody homoconjugates exhibiting anti-neoplastic activity. Applicants respectfully traverse the rejection.

As set forth in the prior Response to Office Action, the cited references do not teach or suggest the claimed homoconjugates having anti-neoplastic activity. First, ***Glennie et al. teaches away from the use of homoconjugates.*** In particular, Glennie relies on bispecificity to bring about its desired effect on the target cell. As is described at page 1, lines 13-30 of Ghettie *et al.*, bispecific antibodies are used in which one specificity is directed to a target cell and another specificity is directed to the desired effector molecule, such as a toxic agent or effector T-cells. Various of such constructs, each having two or three specificities, are described at pages 10-11. Therefore, one of ordinary skill in the art would be taught by Glennie that bispecificity is neccesary to achieve the goals of Glennie. As such, Glennie specifically teaches away from use of homoconjugates and cannot properly be combined with other references concerning the use of homoconjugates.

Similarly, as was described in the prior Response to Office Action, ***all of the conjugates in Ghetie et al. are heteroconjugates***. The reference also fails to suggest homoconjugates. Therefore, again, this reference ***cannot be properly combined with references allegedly suggesting use of homoconjugates***. It is further noted that the anti-neoplastic activity allegedly